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PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing:

12 October 2000 (12.10.00)

International application No.:

PCT/US00/01968

Applicant's or agent's file reference:

48460-PCT

International filing date:

25 January 2000 (25.01.00)

Priority date:

26 January 1999 (26.01.99)

Applicant:

ROSOWSKY, Andre

1. The designated Office is hereby notified of its election made:



in the demand filed with the International preliminary Examining Authority on:

22 August 2000 (22.08.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was



was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 209/82, 403/04, 403/06, 403/12, 473/16, 475/08	A1	(11) International Publication Number: WO 00/59884 (43) International Publication Date: 12 October 2000 (12.10.00)
(21) International Application Number: PCT/US00/01968 (22) International Filing Date: 25 January 2000 (25.01.00) (30) Priority Data: 60/117,321 26 January 1999 (26.01.99) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/117,321 (CIP) Filed on 26 January 1999 (26.01.99) (71) Applicant (for all designated States except US): DANA-FARBER CANCER INSTITUTE, INC. [US/US]; 44 Binney Street, Boston, MA 02115 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): ROSOWSKY, Andre [US/US]; 76 Lindbergh Avenue, Needham, MA 02194 (US). (74) Agents: CORLESS, Peter, F. et al.; Dike, Bronstein, Roberts & Cushman, LLP, 130 Water Street, Boston, MA 02109 (US).		(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PHARMACEUTICALLY ACTIVE COMPOUNDS AND METHODS OF USE THEREOF (57) Abstract The invention relates to pharmaceutically active compounds, and methods of treatment and pharmaceutical compositions that utilize or comprise one or more such compounds. Compounds of the invention are particularly useful for the treatment or prophylaxis of diseases associated with parasitic infection such as toxoplasmosis, cryptosporidiosis, leishmaniasis and malaria.		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/01968

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 209/82, 403/04, 403/06, 403/12, 473/16, 475/08
 US CL : 544/260, 284, 297; 546/276.7; 548/440, 444, 445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/260, 284, 297; 546/276.7; 548/440, 444, 445

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
HURST's "Chemistry of the Pyrimidines, Purines, and Pteridines"Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE substructure search MEDLINE**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHAFI, S.S. ET AL. Studies on biochemically active heterocycles: part II. Synthesis of 2-(1,2,3,4-tetrahydro-9-carbazolylmethyl)thiazolo[3,2-b]-s-triazol-5(6H)-one and related systems. Indian J. Heterocycl. Chem., 1998, Vol. 7 No. 3, pages 231-232, especially compounds 1, 2, 4, and 5, SCHEME-1 and first column page 232.	1, 3, 9
X, P	ROSOWSKY, A. ET AL. Structure-Based Design of Selective Inhibitors of Dihydrofolate Reductase: Synthesis and Antiparasitic Activity of 2,4-Diaminopteridine Analogues with a Bridged Diarylamine Side Chain. J. Med. Chem., 1999, Vol. 42 No. 23 pages 4853-4860, especially compound 4f, page 4858 (English) 1999	1, 3, 6, 9, and 10
X	JP 06-135946 A2 (OTSUKA PHARMA CO. LTD.) 17 May 1994 (17.05.1994), compound 16 on page 18 and compound 24 on page 29	1, 3, 5, and 9
X	KATRITZKY, A.R. ET AL. Chemistry of benzotriazole. Preparation, lithiation and transformation of N-(benzotriazol-1-ylmethyl) heterocycles. 1989, Vol. 26, No. 3, pages 829-36, especially compound 3 Scheme 1 and Tables 1 & 2 on page 830.	1, 3, and 9
X	PRAGST, F. ET AL. Rearrangement of 1-amino-4-methylpyridinium ions into 4-aminomethylpyrimidines under the action of bases, Z. Chem., 1987, Vol. 27, No. 8, pages 289-90, especially compound 3c in Table 1 on page 290.	1, 3, 5, and 9

☒ Further documents are listed in the continuation of Box C.

See patent family annex.

Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search

22 July 2000 (22.07.2000)

Date of mailing of the international search report

22 AUG 2000

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
 Box PCT
 Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Mukund Shah Pat. D.

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/01968

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages -	Relevant to claim No.
X	FELDMAN, ET AL. Some Reactions of Methylene-bis-Amides as Azumono-aldehydes, J.Org.Chem., January 1942, Vol. 7, pages 31-47, especially compound XXV, figure on page 37 and paragraphs 5(I)-5(II) spanning pages 44-45.	1, 3, and 6
X	LUGOVKIN, ET AL. J ORGANIC Chem.USSR (Engl.Transl.), 1964, Vol. VII, pages 1124- especially compound IV figure on page 1124 and second paragraph on page 1126.	1, 3, and 9
X	GB 822,592A (CHEMISCHE FABRIK. PROMONTA. GMBH) 28 October 1959 (28.10.1959), page 2 line 52 to page 3 line 2, page 3 lines 81 to 106, page 4 lines 27 to 56, page 4, lines 93 to 121, page 5 lines 20 to 45, page 6 line 106 to page 7 line 3, page 7 lines 52 to 75, page 7 lines 100 to 125.	1, 3, 5, and 9
A	HURST, Derek T. Chemistry of the Pyrimidines, Purines, and Pteridines, London: John Wiley and Sons, 1980 especially Section (E) pages 168-171 and Section (C) pages 241-242	1, 3-7, 9, and 10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/01968

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 11-18 and 22-26
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1, 3-7, 9, and 10

Remark on Protest

☐
☐

- The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/01968

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) parts of 1, 3-7, 9-10, drawn to Carbazoles.

Group II, claim(s) parts of 1, 3-7, 9-10 drawn to 9-substituted Acridines.

Group III, claim(s) parts of 1, 3-10, drawn to 5-substituted Dibenzazepines.

Group IV, claim(s) parts of 1, 3-7, 9, 11-10, drawn to 5-substituted Dibenzodiazepines.

Group V, claim(s) parts of 1, 3-10, drawn to Phenoxazines.

Group VI, claim(s) parts of 1, 3-10, drawn to Phenothiazines.

Group VII, claim(s) parts of 1, 3-9, 11-10, drawn to Phenazines.

Group VIII, claim(s) parts of 1, 3-10, drawn to all carbon tricyclic compounds.

Group IX, claim(s) parts of 1, 3-9, 11-10, drawn to 11-substituted Dibenzazepines.

Group X, claim(s) parts of 1, 3-9, 11-10, drawn to Dibenzopyrans.

Group XI, claim(s) parts of 1, 3-9, 11-10, drawn to Dibenzothiopyrans.

Group XII, claim(s) parts of 1, 3-7, 9, 11-10, drawn to 10-substituted Acridines.

Group XIII, claim(s) parts of 1-7, 9-10 drawn to N, N-Diphenylamines.

Group XIV, claim(s) parts of 1-7, 9, 11-10, drawn to Diphenylmethanes.

29/1890112

PATENT COOPERATION TREATY


PCT

REC'D 01 JUN 2001

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 48460-PCT		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/01968	International filing date (day/month/year) 25 January 2000 (25.01.2000)	Priority date (day/month/year) 26 January 1999 (26.01.1999)	
International Patent Classification (IPC) or national classification and IPC IPC(7): C07D 209/82, 403/04, 403/06, 403/12, 473/16, 475/08 and US Cl.: 544/260, 284, 297; 546/276; 548/440, 444, 445			
Applicant DANA-FARBER CANCER INSTITUTE, INC.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>6</u> sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u>0</u> sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of report with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand 22 August 2000 (22.08.2000)		Date of completion of this report 13 April 2001 (13.04.2001)	
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer Mukund Shah  Telephone No. (703) 308-1235	

Form PCT/IPEA/409 (cover sheet)(July 1998)

I. Basis of the report**1. With regard to the elements of the international application:***

- ☒ the international application as originally filed.
- ☒ the description:
pages 1-41 _____ as originally filed
pages NONE _____, filed with the demand
pages NONE _____, filed with the letter of _____.
- ☒ the claims:
pages 42-53 _____, as originally filed
pages NONE _____, as amended (together with any statement) under Article 19
pages NONE _____, filed with the demand
pages NONE _____, filed with the letter of _____.
- ☒ the drawings:
pages NONE _____, as originally filed
pages NONE _____, filed with the demand
pages NONE _____, filed with the letter of _____.
- ☐ the sequence listing part of the description:
pages NONE _____, as originally filed
pages NONE _____, filed with the demand
pages NONE _____, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages none
- ☒ the claims, Nos. none
- ☒ the drawings, sheets/~~fig~~ none

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 2, 8, 11-18 and 22-26 and parts of 1, 3-7, 9-10

because:

- ☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require international preliminary examination (*specify*):

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 11-18 and 22-26 are so unclear that no meaningful opinion could be formed (*specify*):

they are multiply dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

- ☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

- ☒ no international search report has been established for said claims Nos. 2, 8, 11-18, & 22-26, and parts of 1, 3-7, 9, and 10.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)

Claims 4, 10

YES

Claims 1, 3, 5-7, 9,

NO

Inventive Step (IS)

Claims 4, 10

YES

Claims 1, 3, 5-7, 9

NO

Industrial Applicability (IA)

Claims 1, 3-7, 9, AND 10

YES

Claims NONE

NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)

Please See Continuation Sheet

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claims 1, 3, and 9 lack novelty under PCT Article 33(2) as being anticipated by SHAFI (Indian J. Heterocyclic Chem.). Compounds 1, 2, 4, and 5 in Scheme-1 on page 232.

Claims 1, 3, and 9 lack an inventive step under PCT Article 33(3) as being obvious over SHAFI (Indian J. Heterocyclic Chem.). For reasons cited above.

Claims 1, 3, 5, and 9 lack novelty under PCT Article 33(2) as being anticipated by JP 6-135946 A2 (OTSUKA PHARMA CO. LTD.). Compound 16 on page 18 and compound 24 on page 29.

Claims 1, 3, 5, and 9 lack an inventive step under PCT Article 33(3) as being obvious over JP 6-135946 A2 (OTSUKA PHARMA CO. LTD.). For reasons cited above.

Claims 1, 3, 5, and 9 lack novelty under PCT Article 33(2) as being anticipated by PRAGST (Z. Chem.). Compound 3c in Table 1 on page 290.

Claims 1, 3, 5, and 9 lack an inventive step under PCT Article 33(3) as being obvious over PRAGST (Z. Chem.). For reasons cited above.

Claims 1, 3, and 6 lack novelty under PCT Article 33(2) as being anticipated by FELDMAN (J. Org. Chem.). Compound XXV on page 37.

Claims 1, 3, and 6 lack an inventive step under PCT Article 33(3) as being obvious over FELDMAN (J. Org. Chem.). For reasons cited above.

Claims 1, 3, and 9 lack novelty under PCT Article 33(2) as being anticipated by LUGOVKIN (J. Organic Chem. USSR Engl. Transl.). Compound IV on page 1124.

Claims 1, 3, and 9 lack an inventive step under PCT Article 33(3) as being obvious over LUGOVKIN (J. Organic Chem. USSR Engl. Transl.). For reasons cited above.

Claims 1, 3, 5, and 9 lack novelty under PCT Article 33(2) as being anticipated by GB 822,592 A (CHEMISCHE FABRIK, PROMONTA, GMBH). Example 1 on page 2, Example 2 on page 3, Example 3 on page 4, Example 4 on page 4, Example 5 on page 5, Example 9 on page 6, Example 10 on page 7, and Example 11 on page 7.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/01968

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Claims 1, 3, 5, and 9 lack an inventive step under PCT Article 33(3) as being obvious over GB 822,592 A (CHEMISCHE FABR PROMONTA, GMBH). For reasons cited above.

Claims 4 and 10 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the compounds of these claims.

Claims 1, 3-7, 9, and 10 meet the criteria set out in PCT Article 33(4), because the compounds have industrial applicability.

PATENT COOPERATION TREATY

RECEIVED

AUG 24 2000

DIKE BRONSTEIN
ROBERTS CUSHMAN

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

From the INTERNATIONAL SEARCHING AUTHORITY

To:
PETER F. CORLESS
DIKE, BRONSTEIN, ROBERTS & CUSHMAN, LLP
130 WATER STREET
BOSTON, MA 02109

Date of Mailing
(day/month/year)

22 AUG 2000

Applicant's or agent's file reference
48460-PCT

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US00/01968

International filing date
(day/month/year)

25 JANUARY 2000 (25.01.2000)

Applicant
DANA-FARBER CANCER INSTITUTE, INC.

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompany sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer

Mukund Shah Ph. D.

Telephone No. (703) 308-1235

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 48460-PCT	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US00/01968	International filing date (<i>day/month/year</i>) 25 JANUARY 2000 (25.01.2000)	(Earliest) Priority Date (<i>day/month/year</i>) 26 JANUARY 1999 (26.01.1999)
Applicant DANA-FARBER CANCER INSTITUTE, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/01968

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 11-18 and 22-26
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1, 3-7, 9, and 10

Remark on Protest

☐
☐

- The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/01968

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 209/82, 403/04, 403/06, 403/12, 473/16, 475/08

US CL : 544/260, 284, 297; 546/276.7; 548/440, 444, 445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/260, 284, 297; 546/276.7; 548/440, 444, 445

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
HURST's "Chemistry of the Pyrimidines, Purines, and Pteridines"

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE substructure search MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHAFI, S.S. ET AL. Studies on biochemically active heterocycles: part II. Synthesis of 2-(1,2,3,4-tetrahydro-9-carbazolylmethyl)thiazolo[3,2-b]-s-triazol-5(6H)-one and related systems. Indian J. Heterocycl. Chem., 1998, Vol. 7 No. 3, pages 231-232, especially compounds 1, 2, 4, and 5, SCHEME-1 and first column page 232.	1, 3, 9
X, P	ROSOWSKY, A. ET AL. Structure-Based Design of Selective Inhibitors of Dihydrofolate Reductase: Synthesis and Antiparasitic Activity of 2,4-Diaminopteridine Analogues with a Bridged Diarylamine Side Chain. J. Med. Chem., 1999, Vol. 42 No. 23 pages 4853-4860, especially compound 4f, page 4858 (English) 1999	1, 3, 6, 9, and 10
X	JP 06-135946 A2 (OTSUKA PHARMA CO. LTD.) 17 May 1994 (17.05.1994), compound 16 on page 18 and compound 24 on page 29	1, 3, 5, and 9
X	KATRITZKY, A.R. ET AL. Chemistry of benzotriazole. Preparation, lithiation and transformation of N-(benzotriazol-1-ylmethyl) heterocycles. 1989, Vol. 26, No. 3, pages 829-36, especially compound 3 Scheme 1 and Tables 1 & 2 on page 830.	1, 3, and 9
X	PRAGST, F. ET AL. Rearrangement of 1-amino-4-methylpyridinium ions into 4-aminomethylpyrimidines under the action of bases, Z. Chem., 1987, Vol. 27, No. 8, pages 289-90, especially compound 3c in Table 1 on page 290.	1, 3, 5, and 9



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

22 July 2000 (22.07.2000)

Date of mailing of the international search report

22 AUG 2000

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/01968

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FELDMAN, ET AL. Some Reactions of Methylene-bis-Amides as Amino-aldehydes, J.Org.Chem., January 1942, Vol. 7, pages 31-47, especially compound XXV, figure on page 37 and paragraphs 5(I)-5(II) spanning pages 44-45.	1, 3, and 6
X	LUGOVKIN, ET AL. J ORGANIC Chem.USSR (Engl.Transl.). 1964, Vol. VII, pages 1124- especially compound IV figure on page 1124 and second paragraph on page 1126.	1, 3, and 9
X	GB 822,592A (CHEMISCHE FABRIK, PROMONTA, GMBH) 28 October 1959 (28.10.1959), page 2 line 52 to page 3 line 2, page 3 lines 81 to 106, page 4 lines 27 to 56, page 4, lines 93 to 121, page 5 lines 20 to 45, page 6 line 106 to page 7 line 3, page 7 lines 52 to 75, page 7 lines 100 to 125.	1, 3, 5, and 9
A	HURST, Derek T. Chemistry of the Pyrimidines, Purines, and Pteridines, London: John Wiley and Sons, 1980 especially Section (E) pages 168-171 and Section (C) pages 241-242	1, 3-7, 9, and 10

Box III TEXT OF THE ABSTRACT (Continuation of Item 5 of the first sheet)

NEW ABSTRACT

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) parts of 1, 3-7, 9-10, drawn to Carbazoles.

Group II, claim(s) parts of 1, 3-7, 9-10 drawn to 9-substituted Acridines.

Group III, claim(s) parts of 1, 3-10, drawn to 5-substituted Dibenzazepines.

Group IV, claim(s) parts of 1, 3-7, 9, 11-10, drawn to 5-substituted Dibenzodiazepines.

Group V, claim(s) parts of 1, 3-10, drawn to Phenoxazines.

Group VI, claim(s) parts of 1, 3-10, drawn to Phenothiazines.

Group VII, claim(s) parts of 1, 3-9, 11-10, drawn to Phenazines.

Group VIII, claim(s) parts of 1, 3-10, drawn to all carbon tricyclic compounds.

Group IX, claim(s) parts of 1, 3-9, 11-10, drawn to 11-substituted Dibenzazepines.

Group X, claim(s) parts of 1, 3-9, 11-10, drawn to Dibenzopyrans.

Group XI, claim(s) parts of 1, 3-9, 11-10, drawn to Dibenzothiopyrans.

Group XII, claim(s) parts of 1, 3-7, 9, 11-10, drawn to 10-substituted Acridines.

Group XIII, claim(s) parts of 1-7, 9-10 drawn to N, N-Diphenylamines.

Group XIV, claim(s) parts of 1-7, 9, 11-10, drawn to Diphenylmethanes.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the letter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.